



## Complete Summary

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### GUIDELINE TITLE

The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer.

### BIBLIOGRAPHIC SOURCE(S)

Breast Cancer Disease Site Group. The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Oct [online update]. 22 p. (Practice guideline report; no. 1-5). [33 references]

### GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the [Cancer Care Ontario Web site](#) for details on any new evidence that has emerged and implications to the guidelines.

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## SCOPE

### DISEASE/CONDITION(S)

Stage IV (metastatic) breast cancer

### GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness  
Treatment

## **CLINICAL SPECIALTY**

Oncology

## **INTENDED USERS**

Physicians

## **GUIDELINE OBJECTIVE(S)**

To evaluate the role of aromatase inhibitors as first-, second- and third-line treatment of postmenopausal women with stage IV (metastatic) breast cancer

## **TARGET POPULATION**

Postmenopausal women with stage IV breast cancer who are candidates for hormonal therapy

## **INTERVENTIONS AND PRACTICES CONSIDERED**

**First-, second-, or third-line hormonal therapy with the following agents:**

1. Anastrozole
2. Tamoxifen
3. Letrozole
4. Megestrol acetate
5. Aminoglutethimide
6. Exemestane

## **MAJOR OUTCOMES CONSIDERED**

- Response rates
  - Complete response
  - Partial response
- Time to progression
- Clinical benefit (includes objective response and stable disease)
- Time to treatment failure (includes time to disease progression, death, or withdrawal from treatment)
- Quality of life
- Survival
- Adverse effects

## **METHODOLOGY**

### **METHODS USED TO COLLECT/SELECT EVIDENCE**

Hand-searches of Published Literature (Primary Sources)  
Hand-searches of Published Literature (Secondary Sources)  
Searches of Electronic Databases

## **DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE**

### **2002 Guideline**

The MEDLINE (from 1966) and CANCERLIT (from 1975) databases were searched to December 2001 using disease-specific terms (breast or mammary, cancer, carcinoma, or neoplasm(s), and metastasis, metastatic, or advanced), treatment-specific terms (anti-aromatase or aromatase inhibitors or endocrine therapy or anastrozole or arimidex or exemestane or aromasin or letrozole or femara or megestrol acetate or aminoglutethimide) and design-specific terms (meta-analysis or randomized controlled trial or randomized controlled trials or random). The searches were not restricted by language of publication. Issue 2 (2002) of the Cochrane Library, the Physician Data Query database, clinical trial and practice guideline Internet sites, conference proceedings from the American Society of Clinical Oncology (ASCO) (1997-2001), the European Society for Medical Oncology (1998-2000) and the San Antonio Breast Cancer Symposium (2000-2001), bibliographies, and personal files were also searched.

An update search of the Medline database and the proceedings of the 2002 American Society of Clinical Oncology meeting were conducted in June 2002, after the practitioner feedback survey.

### **2003 Update**

The original literature search has been updated using MEDLINE and CANCERLIT (through October 2003), the Cochrane Library (Issue 4, 2003), the Physician Data Query database, clinical trial and practice guideline Internet sites, proceedings of the annual meeting of ASCO (2003), proceedings of ESMO (2001-2002), and proceedings of the San Antonio Breast Cancer Symposium (2002).

### **Inclusion Criteria**

Articles were selected for inclusion if they met the following criteria:

- Selective aromatase inhibitors as first-, second- or third-line hormonal therapy in postmenopausal patients with stage IV breast cancer were evaluated using a randomized controlled design, meta-analysis, evidence-based clinical practice guideline format, or noncomparative design (in the absence of randomized controlled trials).
- Reported outcomes of interest included survival, quality of life, tumour response, time to disease progression, and adverse effects of treatment.
- Clinical trial results were reported in either full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and can add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years.

## **Exclusion Criteria**

Articles excluded from this systematic review included:

- Trials of aminoglutethimide (a first-generation aromatase inhibitor) compared to non-aromatase-inhibitor hormonal therapies.
- Trials of fulvestrant, formestane, vorozole or fadrozole, selective aromatase inhibitors that are not available in Ontario.
- Trials of aromatase inhibitors as adjuvant or neo-adjuvant therapy.
- Letters and editorials.

## **NUMBER OF SOURCE DOCUMENTS**

### **2002 Guideline**

Twelve randomized trials, three phase II trials, and three published meta-analyses were reviewed.

### **2003 Update**

The update searches found published reports of updates for two publications that had been included in the original evidence summary: the first was an update to a large randomized trial, and the second was a meta-analysis of individual-patient data from two trials.

## **METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE**

Expert Consensus (Committee)

## **RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE**

Not applicable

## **METHODS USED TO ANALYZE THE EVIDENCE**

Meta-Analysis of Randomized Controlled Trials  
Review of Published Meta-Analyses  
Systematic Review with Evidence Tables

## **DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE**

### **2002 Guideline**

To estimate the overall effect of aromatase inhibitors versus tamoxifen as first-line therapy on response and time to disease progression, data were abstracted from the published reports of individual randomized trials and pooled using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). For the pooled analysis of tumour response, the numbers of patients with a complete or partial response were abstracted from text or tables in published reports, abstracts, or poster presentations. Time-to-progression data were obtained by estimating the number of patients who progressed or died within 12 months after randomization from the Kaplan-Meyer

probability curves presented in each report. These numbers and the numbers randomized were used for the meta-analysis.

Results are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI). For tumour response, a relative risk (RR) >1.0 indicates that patients in the experimental treatment group (aromatase inhibitor) had a higher probability of a complete or partial response compared with those in the control group (tamoxifen); conversely, a relative risk <1.0 favours tamoxifen over the aromatase inhibitor. For disease progression, a relative risk <1.0 indicates that the patients in the experimental treatment group (aromatase inhibitor) experienced delayed progression compared with those in the control group (tamoxifen); a relative risk >1.0 favours tamoxifen over the aromatase inhibitor. The random-effects model was used for pooling across studies in preference to the fixed-effects model, as the more conservative estimate of effect.

Data from second-line trials were not pooled by the guideline developers because a published meta-analysis, based on individual patient data from randomized trials of aromatase inhibitors versus megestrol acetate as second-line therapy, was available.

### **2003 Update**

The information above remains current.

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

### **2002 Guideline**

The Breast Cancer Disease Site Group (DSG) reviewed draft guideline reports at two meetings in 2001. At the first meeting, the discussion centered on the role of aromatase inhibitors versus tamoxifen, which aromatase inhibitor to use, the role of evidence from clinical trials funded by drug companies, and the lack of evidence for second-line treatment options if aromatase inhibitors were to be used as first-line therapy. After reviewing and discussing the evidence, the DSG members had difficulty reaching consensus on recommendations for the use of aromatase inhibitors. They requested that data from the first-line trials be pooled before reviewing the evidence again.

At their next meeting, the DSG considered the optimum dose of letrozole, which is marketed as 2.5-mg tablets, as second-line therapy. It is not clear from the data if the doses evaluated in clinical trials (0.5 and 2.5 mg) are equally effective. The DSG reviewed toxicity data from randomized trials and noted that the rates of thromboembolism favour aromatase inhibitors over tamoxifen but that rates were low with both treatments. They also discussed the use of aromatase inhibitors in premenopausal women, and added the biologic rationale for not treating these patients with aromatase inhibitors to section II of the guideline report. After discussing the role of economic analyses in guideline development, the DSG decided not to include any detailed description of these studies but to list references for them in the guideline report.

The DSG members reviewed the evidence available from the randomized trials and meta-analysis and concluded that there was no clear evidence of a difference in survival between aromatase inhibitors and tamoxifen as first-line therapy. Treatment with aromatase inhibitors, however, was associated with higher objective response rates and prolonged time to progression compared to tamoxifen. When tumour response or time to disease progression is the outcome of interest, the DSG recommended that aromatase inhibitors are an acceptable alternative to tamoxifen as first-line therapy for metastatic breast cancer. During these discussions, DSG members acknowledged that their involvement in a clinical trial of tamoxifen versus exemestane presented a potential conflict of interest that could make them reluctant to recommend aromatase inhibitors in the first-line setting.

The draft guideline report was subsequently reviewed by Cancer Care Ontario's Policy Advisory Committee on New Cancer Drugs, who provided feedback that suggested a stronger recommendation for aromatase inhibitors in the first-line setting. In response to this feedback, the recommendation was revised from "acceptable alternative" to "preferred treatment option" and approved by the Breast Cancer DSG.

### **2003 Update**

The information above remains current.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

Not applicable

## **COST ANALYSIS**

Published cost analyses were reviewed during the preparation of this guideline.

## **METHOD OF GUIDELINE VALIDATION**

External Peer Review  
Internal Peer Review

## **DESCRIPTION OF METHOD OF GUIDELINE VALIDATION**

Practitioner feedback was obtained through a mailed survey of 121 practitioners (81 medical oncologists and 40 radiation oncologists) in Ontario. The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The guideline report and questionnaire were mailed on May 14th, 2002. Follow-up reminders were sent two weeks (post card) and four weeks (complete package mailed again) later. The Breast Cancer Disease Site Group reviewed the results of the survey.

The practice guideline reflects the integration of the draft recommendations with the feedback obtained from the external review process. It has been approved by

the Breast Cancer Disease Site Group and the Practice Guidelines Coordinating Committee.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

#### First-line Therapy

- Anastrozole and letrozole are modestly superior to tamoxifen (in terms of objective response rate and time to disease progression) as first-line therapy for postmenopausal women with stage IV breast cancer and are the preferred treatment option in this setting.
- Tamoxifen remains an acceptable alternative.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

#### Second-line Therapy

- Anastrozole, letrozole, and exemestane are superior to megestrol acetate or aminoglutethimide as second-line hormonal therapy and are the preferred treatment option in this setting.
- There are insufficient data to recommend any one aromatase inhibitor over others in this setting.

#### Third- or Greater-line Therapy

For postmenopausal women with advanced breast cancer who have been heavily pretreated with hormonal agents and chemotherapy, exemestane is an acceptable therapy.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized trials and meta-analyses.

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

- There are three randomized trials comparing anastrozole with tamoxifen, one of letrozole versus tamoxifen and one of exemestane versus tamoxifen as first-line therapy for metastatic breast cancer. Treatment with selective aromatase inhibitors was associated with higher objective response rates and

prolonged time to progression compared to tamoxifen, but definitive survival and quality-of-life data are not available. The toxicity profile of the aromatase inhibitors is acceptable.

- There are three randomized trials comparing letrozole to megestrol acetate or aminoglutethimide, two of anastrozole versus megestrol acetate, and one of exemestane versus megestrol acetate as second-line hormonal therapy for metastatic breast cancer. Women eligible for these trials included those who relapsed during or within 6 months of completion of adjuvant anti-estrogen therapy, and those who progressed on first-line anti-estrogen therapy for metastatic disease. Treatment with selective aromatase inhibitors was associated with equivalent or better objective response rates and time to progression, and a superior toxicity profile, compared to megestrol acetate or aminoglutethimide. Two individual trials and a meta-analysis of individual-patient data from four trials detected a modest but statistically significant survival advantage for aromatase inhibitors, compared to control. There were no consistent differences in measures of quality of life between aromatase inhibitors and control therapy in randomized trials. There were no significant differences between doses of anastrozole of 1.0 and 10 mg, but two of three trials detected significantly higher survival rates with letrozole 2.5 mg compared to 0.5 mg.
- A nonblinded randomized trial of letrozole versus anastrozole, reported only in abstract form, detected a statistically significant increase in response rate with letrozole compared to anastrozole as second-line treatment but no difference in time to progression. No survival or quality-of-life data are available from this trial.
- Data from three phase II trials indicate that exemestane therapy, as third- or greater-line hormonal therapy, is associated with modest but appreciable rates of objective response and is well tolerated. There are no data from clinical trials of other aromatase inhibitors in this setting.

## **POTENTIAL HARMS**

- In randomized trials of anastrozole and letrozole compared to tamoxifen as first-line therapy for metastatic disease, approximately 5% of patients in both treatment groups experienced serious adverse effects that led to withdrawal from the trial. Overall, the patients receiving aromatase inhibitors in these trials reported the same or slightly higher numbers of hot flashes but less vaginal bleeding and fewer thromboembolic events than those receiving tamoxifen. The tumour flare phenomenon was reported with similar frequency for the anastrozole (3.0%) and tamoxifen groups (3.5%) in trials reported by others.
- In trials of anastrozole, letrozole, or exemestane versus megestrol acetate or aminoglutethimide as second-line therapy, serious adverse events leading to study withdrawal were also uncommon. Fewer women receiving aromatase-inhibitor therapy experienced weight gain, dyspnea or thromboembolic events, but more had gastrointestinal symptoms (nausea, vomiting, diarrhea) compared to control.
- Nausea, fatigue, and hot flashes were the most commonly reported adverse effects in the phase II trials of exemestane as third- (or greater-) line therapy.

- Refer to Table 4 in the original guideline document for toxicity data from full reports of clinical trials of selective aromatase inhibitors (percent patients with adverse effects).

## CONTRAINDICATIONS

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Selective aromatase inhibitors are contraindicated in premenopausal women.

## QUALIFYING STATEMENTS

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Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

End of Life Care  
Living with Illness

### IOM DOMAIN

Effectiveness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

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**ADAPTATION**

Not applicable: The guideline was not adapted from another source.

**DATE RELEASED**

2002 Sep 3 (revised online 2003 Oct)

**GUIDELINE DEVELOPER(S)**

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

**GUIDELINE DEVELOPER COMMENT**

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

**SOURCE(S) OF FUNDING**

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

**GUIDELINE COMMITTEE**

Breast Cancer Disease Site Group

**COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE**

For a current list of past and present members, please see the [Cancer Care Ontario Web site](#).

**FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

Members of the Breast Cancer Disease Site Group disclosed information on potential conflict of interest before discussing this practice guideline. DSG members acknowledged that their involvement in a clinical trial of tamoxifen versus exemestane presented a potential conflict of interest that could make them reluctant to recommend aromatase inhibitors in the first-line setting.

**GUIDELINE STATUS**

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## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [Cancer Care Ontario Web site](#).

## **AVAILABILITY OF COMPANION DOCUMENTS**

The following are available:

- The role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO), 2003 Oct. Electronic copies: Available from the [Cancer Care Ontario Web site](#).
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on June 23, 2003. The information was verified by the guideline developer as of July 16, 2003. This summary was updated again on April 19, 2004. The information was verified by the guideline developer on April 29, 2004.

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